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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C12N 9/88, G01N 33/68

A3

(11) International Publication Number: **WO 99/51725**

(43) International Publication Date: 14 October 1999 (14.10.99)

(21) International Application Number: PCT/IL99/00190

(22) International Filing Date: 30 March 1999 (30.03.99)

(30) Priority Data:
123925 2 April 1998 (02.04.98) IL

(71) Applicant *(for all designated States except US)*: YEDA RESEARCH AND DEVELOPMENT CO. LTD. [IL/IL]; Weizmann Institute of Science, P.O. Box 95, 76100 Rehovot (IL).

(72) Inventors; and

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(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report:
2 December 1999 (02.12.99)

(54) Title: ASSAY FOR THE DIAGNOSIS OF SCHIZOPHRENIA BASED ON A NEW PEPTIDE

(57) Abstract

The invention concerns peptides which bind antibodies that are found in elevated levels in body fluids of schizophrenic patients and are found at a lower level or not found at all in body fluids of non–schizophrenic individuals. Using a computerized program, the antigenic epitope of the peptides of the invention is predicted as having a core of hydrophobic amino acids which is surrounded by positively charged amino acids. The peptides of the invention are useful in the diagnosis of schizophrenia in an individual.

FOR THE PURPOSES OF INFORMATION ONLY

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ZW	Zimbabwe

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IL 99/00190

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N9/88 G01N33/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 23970 A (YEDA RES & DEV ;RYCUS AVIGAIL (IL); SHINITZKY MEIR (IL); DECKMANN) 8 September 1995 (1995-09-08) abstract; claims	1,7,8, 12-14
X	WO 94 26107 A (UNIV NEW YORK ;FRIEDHOFF ARNOLD J (US); BASHAM DARYL A (US); MILLE) 24 November 1994 (1994-11-24) abstract; claims	1,7,8, 12-14
X	A. ISHIGURO ET AL: "Identification of candida albicans antigens reactive with immunoglobulin E antibody of human sera" INFECTION AND IMMUNITY, vol. 60, no. 4, 1992, pages 1550-1557, XP002116908 abstract; figure 7	5,6

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 September 1999	13/10/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Cervigni, S

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	BLENNOW K ET AL: "Neuron specific enolase in cerebrospinal fluid: A biochemical marker for neuronal degeneration in dementia disorders?" JOURNAL OF NEURAL TRANSMISSION, vol. 8, no. 3, 1 December 1994 (1994-12-01), pages 183-191, XP002083586 ISSN: 0300-9564 page 188 -page 189 ---	1,5,7,8, 10,12-14
X	S.M. GABRIEL ET AL: "Increased concentration of presynaptic proteins in the cingulate cortex of subjects with schizophrenia" ARCH. GEN. PSYCHIATRY, vol. 54, no. 6, 1997, pages 559-566, XP002116909 abstract; table 3 -----	1,5,7,8, 10,12-14

INTERNATIONAL SEARCH REPORT

rnational application No.
PCT/IL 99/00190

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-4,7
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-4,7

Present claims 1-4 and 7 relate to peptides defined by reference to a desirable characteristic or property, e.g. the capacity of binding to antibodies specific for peptides of Sequences SEQ ID 1-8.
The claims cover all peptides having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such peptides. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the peptides by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely for peptides comprising or consisting of sequences SEQ ID. 1-8, as further specified in claims 5 and 6.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IL 99/00190

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9523970 A	08-09-1995	IL 108789 A	30-10-1998
		AU 695043 B	06-08-1998
		AU 1971695 A	18-09-1995
		BR 9507125 A	30-09-1997
		CA 2184602 A	08-09-1995
		EP 0748447 A	18-12-1996
		JP 9510012 T	07-10-1997
WO 9426107 A	24-11-1994	AU 6913994 A	12-12-1994

PATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
REINHOLD COHN AND PARTNERS
P.O. Box 4060
61040 Tel-Aviv
ISRAEL

RECEIVED
16-02-2000
REINHOLD COHN & PARTNERS

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	09.02.2000
Applicant's or agent's file reference: 11675/1 MM	**REPLY DUE** **within 3 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IL99/00190	30/03/1999	02/04/1998

International Patent Classification (IPC) or both national classification and IPC
C12N9/88

Applicant
YEDA RESEARCH AND DEVELOPMENT CO. LTD. et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain document cited
VII	☒	Certain defects in the international application
VIII	☒	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 02/08/2000.

Name and mailing address of the international preliminary examining authority:
European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer / Examiner
BULCAO DE MELO .., T

Formalities officer (incl. extension of time limits)
Vullo, C
Telephone No. +49 89 2399 2651

I. Basis of the opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*):

Description, pages:

1-27 as originally filed

Claims, No.:

1-14 as originally filed

Drawings, sheets:

1/4-4/4 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-4 and 7,

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-4 and 7.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	8 and 12-14 (NO)
Inventive step (IS)	Claims	5, 6 and 9-11 (YES)
Industrial applicability (IA)	Claims	

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

1. Reference is made to the following documents:

D1: WO-A-23970
D2: Infection and Immunity, Vol. 60, No. 40, 1992, pages 1550-1557

SECTION V

2. Novelty (**Article 33(2) PCT**)

The present application does not satisfy the criterion set forth in **Article 33 (2) PCT** because the subject-matter of **claims 8 and 12-14** is considered to be part of the prior art as defined in the regulations (**Rule 64 (1)-(3) PCT**).

Document **D1** discloses an assay for the diagnosis of schizophrenia as defined in claim 8. It should be noted that the platelet antigen (step b of assay of D1) is specific for schizophrenia, i.e. it is an antigen to which the PAA (platelet-associated antibodies) of schizophrenic patients are directed to. Thus, said platelet antigen is a peptide capable of binding to antibodies that are found in elevated levels in body fluids of schizophrenic patients (i.e. PAA). D1 also discloses a kit for use in said diagnosis assay. (see Abstract, page 2, line 20-page 5, line 6 and claims).

Therefore, the subject-matter of **claims 8 and 12-14** is not new in view of **D1**.

3. Inventive Step (**Article 33 (3) PCT**)

The **technical problem** to be solved by the present application can be considered to lie in the provision of an antigen peptide which binds antibodies that are found in elevated levels in body fluids of schizophrenic patients.

The **solution** provided by the Applicant to solve the above problem is a peptide having one of the sequences SEQ ID NO:1-8.

The **closest prior art** to evaluate the inventiveness of **claims 5, 6 and 9-11** is document **D2**. D2 discloses *Candida albicans* protein allergens which react with IgE antibodies that are present in elevated levels in serum samples of asthmatic patients.

One of the *C. albicans* antigens (part of its sequence) has a significant level of homology with the sequences SEQ ID NO:1-8 of the present application.
(See Abstract and figure 7).

D2 does not disclose nor suggest any relation between said antigens and schizophrenia. Neither D2, nor any of the cited prior art, provides any indication that would teach the person skilled person in the art, with a reasonable expectation of success, to identify sequences SEQ ID NO:1-8 as immunologically active peptides which have high binding activity to schizophrenic derived antibodies.
The peptides of the invention are capable of differentiating between a sample obtained from an individual suffering from schizophrenia and a sample obtained from a non-schizophrenic individual and are therefore useful in the diagnosis of schizophrenia in an individual.

Therefore, in view of the above, the subject-matter of **claims 5, 6 and 9-11** has to be regarded has involving an inventive step.

SECTION VIII

4. The present application does not satisfy the criterion set forth in **Article 6 PCT** because the following claims are not clear.

4.1. A polypeptide (**claims 1-4 and 7**), regarded as a chemical product, should be clearly and unambiguously characterized by technical features, e.g. its amino acid sequence and not only by the result to be achieved (**cf. Guidelines CIII 4.7 and 4.7a**).

4.2. **Claim 8** refers to a general method for the diagnosis of schizophrenia in an individual wherein there is no reference to the specific peptides (claim 6) of the present application, neither are the peptides mentioned in said claim clearly characterized by technical features, e.g. by their amino acid sequence. This renders claim 8 unclear.

4.3. The vague expression "fragment thereof" fails to define said fragment and therefore renders **claim 14** unclear. This expression does not indicate either the region/domain of the antibody to which the fragment corresponds, the function of the fragment, or any particular characteristic/s that the fragment should have.

SECTION VII

5. Contrary to the requirements of **Rule 5.1(a)(ii) PCT**, the relevant background art disclosed in documents **D1 and D2** is not mentioned in the description, nor are these documents identified therein.

********** * **********

6. In case of filling amended claims, the applicant is requested to take account of the above comments.

The attention of the Applicant is drawn to the fact that the application may not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed (**Article 34 (2)(b) PCT** and **Rule 70.2 (c) PCT**).

In order to facilitate the examination of the conformity of the amended application with the requirements of **Article 34 (2)(b) PCT**, the Applicant is requested to clearly identify the amendments carried out, irrespective of whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based.

16

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
11675/.1 MM		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IL99/00190	30/03/1999	02/04/1998
International Patent Classification (IPC) or national classification and IPC C12N9/88		
Applicant YEDA RESEARCH AND DEVELOPMENT CO. LTD. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
10/10/1999	13.07.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer BULCAO DE MELO .., T Telephone No. +49 89 2399 8972

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IL99/00190

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-27 as originally filed

Claims, No.:

1-14 as originally filed

Drawings, sheets:

1/4-4/4 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-4 and 7.

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-4 and 7.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 5, 6 and 9-11
	No:	Claims 8 and 12-14
Inventive step (IS)	Yes:	Claims 5, 6 and 9-11
	No:	Claims
Industrial applicability (IA)	Yes:	Claims 5, 6 and 14
	No:	Claims 8-13 (No Assesment, see Section V, Item 4.2)

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

1. Reference is made to the following documents:

D1: WO-A-23970
D2: Infection and Immunity, Vol. 60, No. 40, 1992, pages 1550-1557

SECTION V

2. Novelty (**Article 33(2) PCT**)

The present application does not satisfy the criterion set forth in **Article 33 (2) PCT** because the subject-matter of **claims 8 and 12-14** is considered to be part of the prior art as defined in the regulations (**Rule 64 (1)-(3) PCT**).

Document **D1** discloses an assay for the diagnosis of schizophrenia as defined in claim 8. It should be noted that the platelet antigen (step b of assay of D1) is specific for schizophrenia, i.e. it is an antigen to which the PAA (platelet-associated antibodies) of schizophrenic patients are directed to. Thus, said platelet antigen is a peptide capable of binding to antibodies that are found in elevated levels in body fluids of schizophrenic patients (i.e. PAA). D1 also discloses a kit for use in said diagnosis assay. (see Abstract, page 2, line 20-page 5, line 6 and claims).

Therefore, the subject-matter of **claims 8 and 12-14** is not new in view of **D1**.

3. Inventive Step (**Article 33 (3) PCT**)

The **technical problem** to be solved by the present application can be considered to lie in the provision of an antigen peptide which binds antibodies that are found in elevated levels in body fluids of schizophrenic patients.

The **solution** provided by the Applicant to solve the above problem is a peptide having one of the sequences SEQ ID NO:1-8.

The **closest prior art** to evaluate the inventiveness of **claims 5, 6 and 9-11** is document **D2**. D2 discloses Candida albicans protein allergens which react with IgE antibodies that are present in elevated levels in serum samples of asthmatic patients. One of the C. albicans antigens (part of its sequence) has a significant level of homology with the sequences SEQ ID NO:1-8 of the present application. (See Abstract and figure 7).

D2 does not disclose nor suggest any relation between said antigens and schizophrenia. Neither D2, nor any of the cited prior art, provides any indication that would teach the person skilled person in the art, with a reasonable expectation of success, to identify sequences SEQ ID NO:1-8 as immunologically active peptides which have high binding activity to schizophrenic derived antibodies.
The peptides of the invention are capable of differentiating between a sample obtained from an individual suffering from schizophrenia and a sample obtained from a non-schizophrenic individual and are therefore useful in the diagnosis of schizophrenia in an individual.

Therefore, in view of the above, the subject-matter of **claims 5, 6 and 9-11** has to be regarded has involving an inventive step.

4. Industrial Applicability (**Article 33(4) PCT**)

4.1. The subject-matter of present **claims 5, 6 and 14** is susceptible of industrial applicability as defined in **Article 33 (4) PCT**.

4.2. For the assessment of the present **claims 8-13** on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

SECTION VIII

5. The present application does not satisfy the criterion set forth in **Article 6 PCT** because the following claims are not clear.

5.1. A polypeptide (**claims 1-4 and 7**), regarded as a chemical product, should be clearly and unambiguously characterized by technical features, e.g. its amino acid sequence and not only by the result to be achieved (**cf. Guidelines CIII 4.7 and 4.7a**).

5.2. **Claim 8** refers to a general method for the diagnosis of schizophrenia in an individual wherein there is no reference to the specific peptides (claim 6) of the present application, neither are the peptides mentioned in said claim clearly characterized by technical features, e.g. by their amino acid sequence. This renders claim 8 unclear.

5.3. The vague expression "fragment thereof" fails to define said fragment and therefore renders **claim 14** unclear. This expression does not indicate either the region/domain of the antibody to which the fragment corresponds, the function of the fragment, or any particular characteristic/s that the fragment should have.

SECTION VII

6. Contrary to the requirements of **Rule 5.1(a)(ii) PCT**, the relevant background art disclosed in documents **D1 and D2** is not mentioned in the description, nor are these documents identified therein.

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

by fax and post

RECEIVED
23-07-2000
REINHOLD COHN & PARTNER

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

To:

REINHOLD COHN AND PARTNERS
P.O. Box 4060
61040 Tel-Aviv
ISRAEL

FAX NO: +972-3-7109.407

Date of mailing *(day/month/year)*	13.07.2000
Applicant's or agent's file reference 11675D1 MM	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IL99/00190	30/03/1999	02/04/1998

Applicant
YEDA RESEARCH AND DEVELOPMENT CO. LTD. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer

Büchler, S

Tel.+49 89 2399-8090

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
11675/.1 MM		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IL99/00190	30/03/1999	02/04/1998
International Patent Classification (IPC) or national classification and IPC C12N9/88		
Applicant YEDA RESEARCH AND DEVELOPMENT CO. LTD. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
10/10/1999	13.07.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer BULCAO DE MELO .., T Telephone No. +49 89 2399 8972

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IL99/00190

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-27 as originally filed

Claims, No.:

1-14 as originally filed

Drawings, sheets:

1/4-4/4 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-4 and 7.

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-4 and 7.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5, 6 and 9-11
	No:	Claims	8 and 12-14
Inventive step (IS)	Yes:	Claims	5, 6 and 9-11
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	5, 6 and 14
	No:	Claims	8-13 (No Assesment, see Section V, Item 4.2)

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

1. Reference is made to the following documents:

D1: WO-A-23970

D2: Infection and Immunity, Vol. 60, No. 40, 1992, pages 1550-1557

SECTION V

2. Novelty (**Article 33(2) PCT**)

The present application does not satisfy the criterion set forth in **Article 33 (2) PCT** because the subject-matter of **claims 8 and 12-14** is considered to be part of the prior art as defined in the regulations (**Rule 64 (1)-(3) PCT**).

Document **D1** discloses an assay for the diagnosis of schizophrenia as defined in claim 8. It should be noted that the platelet antigen (step b of assay of D1) is specific for schizophrenia, i.e. it is an antigen to which the PAA (platelet-associated antibodies) of schizophrenic patients are directed to. Thus, said platelet antigen is a peptide capable of binding to antibodies that are found in elevated levels in body fluids of schizophrenic patients (i.e. PAA). D1 also discloses a kit for use in said diagnosis assay. (see Abstract, page 2, line 20-page 5, line 6 and claims).

Therefore, the subject-matter of **claims 8 and 12-14** is not new in view of **D1**.

3. Inventive Step (**Article 33 (3) PCT**)

The **technical problem** to be solved by the present application can be considered to lie in the provision of an antigen peptide which binds antibodies that are found in elevated levels in body fluids of schizophrenic patients.

The **solution** provided by the Applicant to solve the above problem is a peptide having one of the sequences SEQ ID NO:1-8.

The **closest prior art** to evaluate the inventiveness of **claims 5, 6 and 9-11** is document **D2**. D2 discloses Candida albicans protein allergens which react with IgE antibodies that are present in elevated levels in serum samples of asthmatic patients. One of the C. albicans antigens (part of its sequence) has a significant level of homology with the sequences SEQ ID NO:1-8 of the present application. (See Abstract and figure 7).

D2 does not disclose nor suggest any relation between said antigens and schizophrenia. Neither D2, nor any of the cited prior art, provides any indication that would teach the person skilled person in the art, with a reasonable expectation of success, to identify sequences SEQ ID NO:1-8 as immunologically active peptides which have high binding activity to schizophrenic derived antibodies.
The peptides of the invention are capable of differentiating between a sample obtained from an individual suffering from schizophrenia and a sample obtained from a non-schizophrenic individual and are therefore useful in the diagnosis of schizophrenia in an individual.

Therefore, in view of the above, the subject-matter of **claims 5, 6 and 9-11** has to be regarded has involving an inventive step.

4. Industrial Applicability (**Article 33(4) PCT**)

4.1. The subject-matter of present **claims 5, 6 and 14** is susceptible of industrial applicability as defined in **Article 33 (4) PCT**.

4.2. For the assessment of the present **claims 8-13** on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

SECTION VIII

5. The present application does not satisfy the criterion set forth in **Article 6 PCT** because the following claims are not clear.

5.1. A polypeptide (**claims 1-4 and 7**), regarded as a chemical product, should be clearly and unambiguously characterized by technical features, e.g. its amino acid sequence and not only by the result to be achieved (**cf. Guidelines CIII 4.7 and 4.7a**).

5.2. **Claim 8** refers to a general method for the diagnosis of schizophrenia in an individual wherein there is no reference to the specific peptides (claim 6) of the present application, neither are the peptides mentioned in said claim clearly characterized by technical features, e.g. by their amino acid sequence. This renders claim 8 unclear.

5.3. The vague expression "fragment thereof" fails to define said fragment and therefore renders **claim 14** unclear. This expression does not indicate either the region/domain of the antibody to which the fragment corresponds, the function of the fragment, or any particular characteristic/s that the fragment should have.

SECTION VII

6. Contrary to the requirements of **Rule 5.1(a)(ii) PCT**, the relevant background art disclosed in documents **D1 and D2** is not mentioned in the description, nor are these documents identified therein.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
REINHOLD COHN AND PARTNERS
P.O. Box 4060
61040 Tel-Aviv
ISRAEL

RECEIVED
19 -10- 1999
REINHOLD COHN & PARTNERS

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

18 'o N13 2/11/99

Applicant's or agent's file reference 116750.1 MM	Date of mailing *(day/month/year)* 13/10/1999
	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/IL 99/00190	International filing date *(day/month/year)* 30/03/1999
Applicant YEDA RESEARCH AND DEVELOPMENT CO. LTD. et al.	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Barbara Klaver

Form PCT/ISA/220 (July 1998)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international pbulication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
116750.1 MM		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IL 99/00190	30/03/1999	02/04/1998
Applicant		
YEDA RESEARCH AND DEVELOPMENT CO. LTD. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[X] contained in the international application in written form.

[X] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[X] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[X] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[X] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL 99/00190

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-4, 7
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-4,7

Present claims 1-4 and 7 relate to peptides defined by reference to a desirable characteristic or property, e.g. the capacity of binding to antibodies specific for peptides of Sequences SEQ ID 1-8.
The claims cover all peptides having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such peptides. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the peptides by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely for peptides comprising or consisting of sequences SEQ ID. 1-8, as further specified in claims 5 and 6.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
T/IL 99/00190

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9523970 A	08-09-1995	IL 108789 A	30-10-1998
		AU 695043 B	06-08-1998
		AU 1971695 A	18-09-1995
		BR 9507125 A	30-09-1997
		CA 2184602 A	08-09-1995
		EP 0748447 A	18-12-1996
		JP 9510012 T	07-10-1997
WO 9426107 A	24-11-1994	AU 6913994 A	12-12-1994

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IL 99/00190

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N9/88 G01N33/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 23970 A (YEDA RES & DEV ;RYCUS AVIGAIL (IL); SHINITZKY MEIR (IL); DECKMANN) 8 September 1995 (1995-09-08) abstract; claims	1,7,8, 12-14
X	WO 94 26107 A (UNIV NEW YORK ;FRIEDHOFF ARNOLD J (US); BASHAM DARYL A (US); MILLE) 24 November 1994 (1994-11-24) abstract; claims	1,7,8, 12-14
X	A. ISHIGURO ET AL: "Identification of candida albicans antigens reactive with immunoglobulin E antibody of human sera" INFECTION AND IMMUNITY, vol. 60, no. 4, 1992, pages 1550-1557, XP002116908 abstract; figure 7	5,6

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 September 1999	13/10/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Cervigni, S

Form PCT/ISA/210 (second sheet) (July 1992)

International Application No
PCT/IL 99/00190

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication where appropriate, of the relevant passages	Relevant to claim No.
X	BLENNOW K ET AL: "Neuron specific enolase in cerebrospinal fluid: A biochemical marker for neuronal degeneration in dementia disorders?" JOURNAL OF NEURAL TRANSMISSION, vol. 8, no. 3, 1 December 1994 (1994-12-01), pages 183-191, XP002083586 ISSN: 0300-9564 page 188 -page 189 ---	1,5,7,8, 10,12-14
X	S.M. GABRIEL ET AL: "Increased concentration of presynaptic proteins in the cingulate cortex of subjects with schizophrenia" ARCH. GEN. PSYCHIATRY, vol. 54, no. 6, 1997, pages 559-566, XP002116909 abstract; table 3 -----	1,5,7,8, 10,12-14

1

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
116750.1 MM		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IL 99/00190	30/03/1999	02/04/1998
Applicant		
YEDA RESEARCH AND DEVELOPMENT CO. LTD. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[X] contained in the international application in written form.

[X] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[X] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[X] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[X] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL 99/00190

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-4,7
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-4,7

Present claims 1-4 and 7 relate to peptides defined by reference to a desirable characteristic or property, e.g. the capacity of binding to antibodies specific for peptides of Sequences SEQ ID 1-8.
The claims cover all peptides having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such peptides. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the peptides by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely for peptides comprising or consisting of sequences SEQ ID. 1-8, as further specified in claims 5 and 6.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No
[redacted]/IL 99/00190

A. CLASSIFICATION OF SUBJECT MAT[redacted]
IPC 6 C12N9/88 G01N33/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 23970 A (YEDA RES & DEV ;RYCUS AVIGAIL (IL); SHINITZKY MEIR (IL); DECKMANN) 8 September 1995 (1995-09-08) abstract; claims	1,7,8, 12-14
X	WO 94 26107 A (UNIV NEW YORK ;FRIEDHOFF ARNOLD J (US); BASHAM DARYL A (US); MILLE) 24 November 1994 (1994-11-24) abstract; claims	1,7,8, 12-14
X	A. ISHIGURO ET AL: "Identification of candida albicans antigens reactive with immunoglobulin E antibody of human sera" INFECTION AND IMMUNITY, vol. 60, no. 4, 1992, pages 1550-1557, XP002116908 abstract; figure 7	5,6

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 September 1999	13/10/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Cervigni, S

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Form PCT/ISA/210 (second sheet) (July 1992)

International Application No
[redacted]/IL 99/00190

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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X	S.M. GABRIEL ET AL: "Increased concentration of presynaptic proteins in the cingulate cortex of subjects with schizophrenia" ARCH. GEN. PSYCHIATRY, vol. 54, no. 6, 1997, pages 559-566, XP002116909 abstract; table 3 -----	1,5,7,8, 10,12-14

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
[redacted]/IL 99/00190

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9523970 A	08-09-1995	IL 108789 A	30-10-1998
		AU 695043 B	06-08-1998
		AU 1971695 A	18-09-1995
		BR 9507125 A	30-09-1997
		CA 2184602 A	08-09-1995
		EP 0748447 A	18-12-1996
		JP 9510012 T	07-10-1997
WO 9426107 A	24-11-1994	AU 6913994 A	12-12-1994

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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C12N 9/88, G01N 33/68

A2

(11) International Publication Number: WO 99/51725

(43) International Publication Date: 14 October 1999 (14.10.99)

(21) International Application Number: PCT/IL99/00190

(22) International Filing Date: 30 March 1999 (30.03.99)

(30) Priority Data:
123925 2 April 1998 (02.04.98) IL

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(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: ASSAY FOR THE DIAGNOSIS OF SCHIZOPHRENIA BASED ON A NEW PEPTIDE

(57) Abstract

The invention concerns peptides which bind antibodies that are found in elevated levels in body fluids of schizophrenic patients and are found at a lower level or not found at all in body fluids of non–schizophrenic individuals. Using a computerized program, the antigenic epitope of the peptides of the invention is predicted as having a core of hydrophobic amino acids which is surrounded by positively charged amino acids. The peptides of the invention are useful in the diagnosis of schizophrenia in an individual.

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ASSAY FOR THE DIAGNOSIS OF SCHIZOPHRENIA BASED ON A NEW PEPTIDE

FIELD OF THE INVENTION

The present invention is generally in the field of assays for the diagnosis of mental disorders. More specifically, the present invention provides an assay for the diagnosis of schizophrenia.

PRIOR ART

The following is a list of prior art publications referred to in the present specification.

1. Carpenter, W.T., and Buchanan, R.W., *Review, N. Engl. J. Med.*, **330**681-690, 1994.

2. Knight, J.G., *Find. Exp. Clin. Pharmacol.*, **6**:395-408, 1984.

3. De Lisi, L.E., and Crow, T.J., *Psychiatr. Clin. North Am.*, **9**:115-132, 1987.

4. Ganguli, R., Rabin, B.S., Kelly, R.H., Lyte, M. and Ragu, U., *Ann. N.Y. Acad. Sci.*, **496**:676-690, 1987.

5. Shinitzky, M., Deckmann, M., Kessler, A., Sirota, P., Rabbs, A. and Elizur, A., *An. N.Y. Acad. Sci.*, **621**:205-217, 1991.

6. Deckmann, M., Shinitzky, M., Leykin, I., Cheng, D., Guy, J., Avnon, M., Salganik, I., Amiri, Z., Schlossberg, A., Leibu, E., and Rafael, C., *The Italian J. Psychiatr. Behav. Sci.*, **6**:29-34, 1996.

7. PCT Patent Application Publication Number WO 95/23970.

The acknowledgement herein of the above art should not be construed as an indication that this art is in any way relevant to the patentability of the invention as defined in the appended claims.

The above publications will be acknowledged in the following by indicating their number from the above list.

BACKGROUND OF THE INVENTION

Schizophrenia is a syndrome which encompasses a variety of mental symptoms like auditory hallucinations, paranoia, delusions, catatonia, bizarre behavior or emotional withdrawal. Schizophrenia affects about 1% of the total population and its economical as well as social burden on society are enormous. The onset of the disease occurs at an early age and thus patients typically need life-long medical and psychiatric supervision. Schizophrenia is, therefore, rated as one of the most costly diseases in the industrial world[1].

There are various known risk factors associated with schizophrenia such as genetic predisposition, birth during winter and complications during pregnancy and birth. Viral infections and subsequent autoimmune reactions have also been proposed as possible causative factors[2-4]. The involvement of autoantibodies against platelets in schizophrenic patients was also shown as elevated levels of autoantibodies were detected in schizophrenic and demented patients as compared to control subjects, bipolar, depressed, personality disordered or schizoeffective patients[5-6]. Western Blot analysis revealed a pattern of platelet antigens recognized by autoantibodies obtained from schizophrenic patients which differed from that recognized by autoantibodies obtained from patients suffering from autoimmune thrombocytopenia and dementia[7]. The antigen bound specifically by autoantibodies obtained from schizophrenic patients has been characterized by its molecular weight.

SUMMARY OF THE INVENTION

In accordance with the invention, several proteins which bind autoantibodies that are found in elevated levels in body fluids of schizophrenic patients have been identified. The antibodies which these proteins bind are typically platelet associated autoantibodies (PAA). Such autoantibodies obtained from schizophrenic patients (hereinafter "*schizophrenic derived antibodies – SDA*") were shown to bind the above antigens while autoantibodies obtained from control non-schizophrenic individuals (hereinafter "*non-schizophrenic derived antibodies - NSDA*") did not.

The proteins which were shown to be capable of binding SDA were identified and further characterized by chemical and enzymatic methods. Some of the identified immuno-reactive proteins are known proteins such as glyceraldehyde-3-phosphate dehydrogenase (G3PD), enolase, keratin, hepatocyte growth factor, extracellular calcium sensing receptor and several more. By digesting the rabbit protein enolase, an immunologically active peptide was revealed which had a high binding activity to SDAs.

The revealed peptide, being the immunologically active epitope of the enolase protein, comprised twenty eight amino acids of the following sequence:

SGETEDTFIADLVVGLCTGQIKTGAPCR (Seq. ID No. 1)

On the basis of the revealed peptide, additional peptides were synthesized and highly active ones (i.e. such which had a high binding activity to SDAs as compared to a very low binding activity to NSDA or which do not bind NSDA at all) were identified. Moreover, the synthesized active peptides were capable of differentiating for the first time between plasma samples obtained from schizophrenic patients and plasma samples obtained from control non-schizophrenic individuals.

Further analysis of one of the synthesized highly active peptides (Seq. ID No. 2) showed that this peptide forms a ring via two cysteins and a

dimer via the remaining free cystein. The peptide in this form is most active in its ability to bind SDA.

As described below, the antigenic epitope of the synthetic highly active peptides of the invention seems to be a three dimensional spatial eptiope.

The present invention thus provides a peptide which binds antibodies that are found in elevated levels in body fluids of schizophrenic patients.

The invention further provides a peptide capable of binding antibodies that are found in elevated levels in body fluids of schizophrenic patients, wherein the peptide binds antibodies that are capable of specific binding to a peptide having the following amino acid sequence: LVVGLCTCQIKTGPAC (I.D. No. 2). Several non-limiting examples of such peptides are the following:

iii. IADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 3)

iv. ADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 4)

v. DLVVGLCTGQIKTGAPCR (Seq. I.D. No. 5)

vi. LVVGLCTGQIKTGAPCR (Seq. I.D. No. 6)

vii. LVVGLCTGQIKTGPACR (Seq. I.D. No. 7)

viii. LVVGLCTPQIKTGPACR (Seq. I.D. No. 8)

The invention also provides a peptide which is capable of binding antibodies that are found in elevated levels in body fluids of schizophrenic patients, such peptides capable of binding antibodies which do not bind to peptides selected from the group consisting of :

i. SGETEDTFIADLVVGLCTGQ (Seq. I.D. No. 9)

ii. VVGLCTGQIKTGAPCR (Seq. I.D. No. 10)

iii. CTGQIKTGAPCR (Seq. I.D. No. 11)

iv. LVVGLCTGQIKTGAPC (Seq. ID. No. 12)

v. LVVGLCTGQIKTGAP (Seq. ID No. 13)

vi. LVVGLCTGQIKTGPAC (Seq. ID No. 14)

The invention also provides a peptide capable of binding to antibodies that are found in elevated levels in body fluids of schizophrenic patients comprising an amino acid sequence selected from the group, consisting of:

i. SGETEDTFIADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 1)
ii. LVVGLCTCQIKTGPAC (Seq. I.D. No. 2)
iii. IADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 3)
iv. ADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 4)
v. DLVVGLCTGQIKTGAPCR (Seq. I.D. No. 5)
vi. LVVGLCTGQIKTGAPCR (Seq. I.D. No. 6)
vii. LVVGLCTGQIKTGPACR (Seq. I.D. No. 7)
viii. LVVGLCTPQIKTGPACR (Seq. I.D. No. 8)

By a preferred embodiment the invention provides a peptide capable of binding antibodies that are found in elevated levels in body fluids of schizophrenic patients selected from the group consisting of:

i. SGETEDTFIADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 1)
ii. LVVGLCTCQIKTGPAC (Seq. I.D. No. 2)
iii. IADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 3)
iv. ADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 4)
v. DLVVGLCTGQIKTGAPCR (Seq. I.D. No. 5)
vi. LVVGLCTGQIKTGAPCR (Seq. I.D. No. 6)
vii. LVVGLCTGQIKTGPACR (Seq. I.D. No. 7)
viii. LVVGLCTPQIKTGPACR (Seq. I.D. No. 8)

The letters used above (and hereinafter) to denote specific a.a. are in accordance with the one-letter amino acid (a.a.) symbols recommended by the IUPAC-IUB Biochemical Nomenclature Commission.

Without being bound by theory, on the basis of the results obtained in accordance with the invention, it has become clear that the structure of the antigenic epitope of the peptides to which SDAs are capable of binding at a substantially higher degree as compared to NSDAs is a

three-dimensional epitope. By using a computerized program based on minimal energy calculations, the antigenic epitope of a peptide in accordance with the invention is predicted as being a cyclic structure comprising a hydrophobic core and an extension having about two positive charges. The positive charged extensions may be positioned in one of many possible spatial orientations.

The binding activity of the peptide of the invention to various antibodies may be determined by any of the methods known *per se* such as ELISA or Western Blotting. For example, a tested peptide may be analyzed for its binding activity to antibodies by subjecting it to polyacrylamide gel electrophoresis, blotting it onto PVDS membranes which are then reacted with SDA and compared to their reaction with NSDA.

The extent of binding of the peptides of the invention to PAA can be determined by using any detection system known in the art such as antibodies against human immunoglobulin or fragments thereof linked to a detectable marker. The marker may be a radioactive group, a fluorescent group, an enzyme capable of catalyzing a reaction yielding a detectable product, a biotin group capable of being detected by avidin, etc.

By a preferred embodiment of this aspect, the peptides of the invention are bound onto a solid support such as e.g. a PVDF membrane, reacted with the tested sample and the level of binding of the PAAs in the sample is determined using an anti-human Fc antibody conjugated to a detectable marker.

In accordance with a particular embodiment, the determination of the level of autoantibodies bound to a tested peptide is determined by using anti-human Fc conjugated to horseradish peroxidase (SIGMA) and Fast-DAB™ (SIGMA) or 4-Chloro-naphthol (SIGMA) as the color reagent.

In order for the binding of the tested peptide in accordance with the invention to SDA to be considered *"substantially higher"* than its binding to NSDA, the level of binding to SDA should be statistically significantly

higher than its binding to NSDA as determined by any of the statistical methods known in the art (e.g. Students' t-Test) which are used in connection with results obtained by the experimental methods mentioned above.

Analogs of all the above peptides also form an aspect of the present invention. As will be appreciated by any person versed in the art, the amino acid sequence of the peptides of the invention may be altered, for example by addition, replacement or deletion of one or more amino acids without substantially altering the binding capacity of the peptide to SDAs. Thus for example the leucine positioned in the first position of the amino acid sequence of a peptide of the invention may be substituted by the amino acid glycine or valine which belong to the same family of amino acids without altering the binding activity of the peptide. A person versed in the art will have no difficulty in determining by which amino acid each of the amino acids of the peptide may be replaced in accordance with the known grouping of amino acids into families as may be found, for example, in Molecular Biology of the Cell Editors Alberts B. *et al.*, Garland Publishing, Inc., New York and London, 2nd Edition, 1989, pages 54-55.

Analogs which fall under the scope of the peptides of the present invention are such which have substantially the same level of binding activity to SDAs, as the peptides i.e. have a higher level of binding to SDAs as compared to NSDAs as determined by any of the methods known in the art such as for example that described in Example 1 below.

The peptide of the invention may be obtained by enzymatic digestion (e.g. using Clostrapain) or chemical (CNBr) digestion of a longer protein. In such a case, the resulting peptides are separated by methods known in the art such as by RP-HPLC and the separate peptides may then be used for sequencing (e.g. by Eurosequence b.v. (Nijenborgh 4; 9749 Gronigen; The Netherlands)) and analyzed for their binding capability to SDAs as described above.

Peptides in accordance with the invention may also be synthesized by methods known in the art such as on Abimed 522 at a 10 μmol scale by Eurosequence b.v. (see detailed explanation in the examples below). The binding activity of the newly synthesized peptides will be determined using any of the assays mentioned above.

The peptides of the invention are capable of differentiating between a sample obtained from an individual suffering from schizophrenia and a sample obtained from a non-schizophrenic individual and are therefore useful in the diagnosis of schizophrenia in an individual. Thus, by another of its aspects, the present invention provides a peptide for use in the diagnosis of schizophrenia in an individual, said peptide capable of binding antibodies that are found in elevated levels in body fluids of schizophrenic patients.

The sample of the individual to be tested is typically a PAA containing fraction of a blood sample comprising platelets. However, in accordance with the present invention it has become possible for the first time to determine the probability of existence of schizophrenia in a plasma sample taken from tested individuals without the need to first isolate PAA from the sample. Thus, in accordance with the invention, the sample of an individual to be tested may either be a plasma sample or a PAA containing fraction obtained therefrom by any of the methods known in the art (e.g. by obtaining a platelet-rich plasma (PRP) and isolating PAA therefrom).

Since the peptides of the invention are capable of binding to a different extent to platelet derived autoantibodies in a sample obtained from a schizophrenic patient as compared to a sample obtained from a control non-schizophrenic individual, the peptides may be used in an assay for diagnosis of schizophrenia in an individual. Therefore, the present invention by an additional aspect provides an assay for the diagnosis of schizophrenia in an individual, comprising the following steps:

(a) obtaining a sample from said individual being a blood sample, a platelet-containing fraction thereof, or a fraction containing platelet-associated antibodies (PAA) shed from the platelets;

(b) contacting said sample with a peptide capable of binding to antibodies that are found in elevated levels in body fluids of schizophrenic patients.

(c) determining the level of binding of said peptide to said sample, a level higher than the binding level of said peptide to a sample from non-schizophrenic individuals indicating that said individual has a high likelihood of having schizophrenia.

By a further embodiment the peptide of step (b) above is a peptide which binds antibodies that are capable of specific binding to a peptide having the amino acid sequence of Seq. ID. No. 2. By another embodiment the peptide in step (b) above comprises an a.a. sequence selected from the group consisting of:

i. SGETEDTFIADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 1)
i. LVVGLCTCQIKTGPAC (Seq. I.D. No. 2)
iii. IADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 3)
iv. ADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 4)
v. DLVVGLCTGQIKTGAPCR (Seq. I.D. No. 5)
vi. LVVGLCTGQIKTGAPCR (Seq. I.D. No. 6)
vii. LVVGLCTGQIKTGPACR (Seq. I.D. No. 7)
viii. LVVGLCTPQIKTGPACR (Seq. I.D. No. 8)

By a preferred embodiment, the peptide in step (b) is a peptide selected from the group consisting of:

i. SGETEDTFIADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 1)
ii. LVVGLCTCQIKTGPAC (Seq. I.D. No. 2)
iii. IADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 3)
iv. ADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 4)
v. DLVVGLCTGQIKTGAPCR (Seq. I.D. No. 5)

vi. LVVGLCTGQIKTGAPCR (Seq. I.D. No. 6)

vii. LVVGLCTGQIKTGPACR (Seq. I.D. No. 7)

The present invention also provides a kit useful in the above assay. The kit of the invention comprises a support comprising one or more peptides of the invention immobilized onto it and an anti-human immunoglobulin antibody or fragment thereof. The anti-HIG antibody may be conjugated to a detectable marker or alternatively, the kit may also comprise a second type of antibodies directed against said first antibodies, wherein the second antibodies are conjugated to a detectable marker. The kit will also comprise various reagents required for carrying out the assay as well as instructions for use.

The invention will now be illustrated in the following non-limiting description of specific embodiments and accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a graphical representation showing binding activity of the Peptide 14 having Seq. I.D. No. 2 to PAAs prepared from samples obtained from schizophrenic patients (Fig. 1A) and non-schizophrenic individuals (Fig. 1B). The peptide having Seq. I.D. No. 9 was used as a negative control.

Fig. 2 is a graphical representation showing binding activity of peptide 14 (Seq. I.D. No. 2) to plasma samples obtained from schizophrenic patients (Fig. 2A) and non- schizophrenic individuals (Fig. 2B). The peptide having Seq. I.D. No. 9 was used as a negative control.

Fig. 3 is a graphical representation showing a schematically predicted three-dimensional structure of the antigenic epitope of the peptides of the invention as determined by a computerized program based on minimal energy calculations.

Fig. 4 is an x-ray of a three-dimensional structure of enolase generated from a public peptide database and compared with the water model of the peptides of the invention.

The amino acids found to exist in the epitope are marked as follows:

L = leucine

A = alanine

P = proline

R = arginine

K = hystidine

EXAMPLES

Materials and Methods

1. Platelets and anti-platelet autoantibodies

Venous blood (20 ml) was drawn with heparin as anticoagulant from patients and control subjects. Platelet rich plasma (PRP) was obtained by centrifugation (100 g for 20 mins) at room temperature. Plasma free platelets were obtained by washing them three times with phosphate buffered saline (PBS) supplemented with 10 ml mM EDTA as anticoagulant (4000 g; 15 mins; 4°C). For the isolation of anti-platelet antibodies, the platelets were incubated with 0.1 M glycine/10 mM EDTA, pH 2.8, for 10 min. at room temperature and then centrifuged (4000 g; 15 min; 4°C). The supernatant containing the anti-platelet antibodies, was neutralized with saturated Na_2PO_4 solution and stored at -20 until use.

2. Preparative isoelectric focusing

Platelet concentrates of blood group 0 were purchased from a local blood bank and washed three to five times with PBS/10 mM EDTA (4000 g; 15 min; 4°C) until the supernatant was free of plasma. The platelets (about 20 concentrates) were first solubilized with 20 ml 0.5% Triton X-100/0.5%

NP40 in water for 15 min. at room temperature under gentle shaking. The suspension was centrifuged (10000 g, 15 min. 4°C), the supernatant removed and the pellet two more times extracted with 0.1% Triton X-100 in water. The three supernatants were combined and Ampholyte™ 3/10 (BioRad) was added to a final concentration of 1%. This solution was loaded into the ROTOFOR™ chamber (capacity 60 ml) and the preparative isoelectric focusing was then performed according to the instruction manual of the manufacturer (BioRad). Typically, the focusing was finished after 4.5 h (10°C; 10 Watt constant power). Twenty fractions were harvested and the pH of the fractions determined (pH gradient 1.5-12). The fractions were stored at -20°C until further use.

3. Identification of immuno-reactive fractions

The fractions were analyzed for immuno-reactivity by polyacrylamide (10%) gel electrophoresis, blotting the proteins onto PVDF membranes and probing the membrane with 1 ml auto-antibodies in 50 ml incubation buffer. Anti-human Fc conjugated to horseradish peroxidase (goat) from SIGMA (1:500 dilution) and Fast-DAB™ (SIGMA) or 4-Chloro-naphthol (SIGMA) were used as color reagent in order to detect bound human anti-platelet antibodies. Immuno-reactivity was observed in the fractions with a pH ranging from 6.0 to 10.0.

4. Preparative polyacrylamide (8%) gel electrophoresis

The immuno-reactive fractions (pH 6-10) were combined and separated according to molecular weight under reducing conditions by preparative SDS polyacrylamide gel (8% and 8 cm height) in a PrepCell from BioRad according to the instruction manual of the manufacturer. Fractions (n=400) of 1.5 ml were collected: every tenth fraction was analyzed by SDS

gel electrophoresis followed by silver staining to determine the molecular weight distribution in the 400 fractions.

5. Identification of immuno-reactive fractions

Every fifth fraction (0.1 ml) was dot blotted onto PVDF membranes using the DotBlot device (96 wells) from BioRad. Immuno-reactive fractions were then detected as described above (1.3)

6. Identification of immuno-reactive proteins

As described previously, a variety of immuno-reactive proteins were identified. Priority for sequencing was given to proteins with a high ratio of reactivity to protein amount. Preparation of sample was typically done in the following way: The fractions (+/- 10) around a positive fraction were re-analyzed as described above under 1.5. The positive fractions were combined, lyophilized, re-separated on an analytical (0.75 mm) SDS polyacrylamide (10%) gel and stained with Coomassie Blue. The band was excised and sent to Eurosequence b.v. (enzymatic digestion, RP-HPLC separation of peptides followed by amino acid sequencing).

7. Identification of immuno-reactive epitope

Of the identified proteins, two were found to be commercially available:

a) Glyceraldehyde-6-phosphate dehydrogenase (G6PD)

b) Enolase

About 10 mg protein was digested either enzymatically (Clostrapain) or chemically (CNBr) and the resulting peptides were separated by RP-HPLC. Aliquot (20%) of all fractions were sent by Eurosequence b.v. to the Main Inventor for analysis of immuno-reactivity as described under 1.5. Only the enzymatic digest of the Enolase resulted in an active fragment which was subsequently sequenced by Eurosequence b.v.

8. Peptide synthesis

Various peptides were synthesized on Abimed 522 at a 10 micromol scale by Eurosequence b.v. Peptides were routinely dissolved in 1 ml water/DMF/DMSO (1:1:1;v/v/v). Peptides were line-blotted onto PVDF membranes and tested for immuno-reactivity as described above.

9. Epitope scanning

Water models of the peptides of the invention were calculated on a MacIntosh computer system. An x-ray three dimensional structure of enolase was generated from a public peptide database and the surface of the enolase was scanned to find epitopes which match the epitopes of the peptides calculated by the water model.

EXAMPLE 1: Identification of immuno-reactive proteins

The following proteins have been identified as such capable of binding autoantibodies present in high levels in schizophrenic patients at a high level as determined by the assay described in 1.3 above:

Protein:

Glyceraldehyde-6-phosphate dehydrogenase
Enolase
Keratin
Hepatocyte growth factor
Extracellular calcium sensing receptor

The above identified proteins were tested for their binding capability to plasma samples obtained from schizophrenic patients and to plasma samples obtained from control non-schizophrenic patients. The results showed that it was not possible to use the above proteins to discriminate between a plasma sample obtained from a schizophrenic patient and that

obtained from a non-schizophrenic individual, i.e. the binding results were not conclusive.

The binding activity of the above two enzymes was then tested by reacting them with SDAs (prepared from samples obtained from schizophrenic patients) and to NSDA (prepared from control non-schizophrenic individuals). As seen in Table 1 below, in this case binding of the proteins to SDAs was substantially higher than their binding to NSDAs expressed by the number of samples that reacted positively with each of the enzymes.

Table 1

Reactivity of proteins to SDAs and NSDAs

Enzyme	Patients (n=8)	Controls (n=8)
	Positive	Positive
G-3-P-Dehydrogenase		
from **human**	7/8	1/8
from **pig**	8/8	1/8
from **chicken**	7/8	2/8
from **yeast**	6/8	1/8
from **bacillus subtilis**	1/8	2/8
Enolase		
from **Rabbit**	7/8	1/8

The above results showed that the proteins obtained in accordance with the invention may be useful in the diagnosis of schizophrenia in a tested individual but require that the sample obtained and tested from the individual will comprise of prepared platelet-derived autoantibodies. The enzymes are not suitable for detecting schizophrenia directly in a plasma sample.

EXAMPLE 2: Identification of the epitope in the digested proteins capable of specific binding to SDAs:

Chemical (CNBr) and enzymatic digestions (Clostrapain) of human G-3-P-Dehydrogenase and rabbit Enolase were used to identify the epitope. Only the enzymatic digest of the Enolase revealed one peptide which was immunologically active (amino acids 372-399; The peptide having Seq. I.D. No. 1 in the following Table 2), i.e. was capable of binding SDAs to a higher extent and its capability of binding to NSDAs.

Based on the sequence of the epitope identified in the digested proteins, a number of peptides were synthesized by the method described in 1.8 above. The synthesized peptides were then evaluated for their binding activity to SDAs as compared to NSDAs as described above.

As seen in Table 2 below, several of the synthesized peptides showed a substantially higher binding activity to SDAs as compared to their binding to NSDAs (indicated as **YES** in the table) while others showed no significant differences in their binding to samples from schizophrenic and non-schizophrenic individuals (designed as **no** in the table).

Table 2

Peptide		Seq. I.D.No.	Activity
SGETEDTFIADLVVGLCTGQIKTGAPCR	(28aa)	1	YES
LVVGLCTCQUKTGPAC	(17aa)	2	YES
IADLVVGLCTGQIKTGAPCR	(20aa)	3	YES
ADLVVGLCTGQIKTGAPCR	(19aa)	4	YES
DLVVGLCTGQIKTGAPCR	(18aa)	5	YES
LVVGLCTGQIKTGAPCR	(17aa)	6	YES
LVVGLCTGQUKTGPACR	(17aa)	7	YES
LVVGLCTPQUKTGPACR	(17aa)	8	YES
SGETEDTFIADLVVGLCTGQ	(20aa)	9	No
VVGLCTGQIKTGAPCR	(16aa)	10	No
CTGQIKTGAPCR	(12aa)	11	No
LVVGLCTGQIKTGAPC	(16aa)	12	No
LVVGLCTGQIKTGAP	(15aa)	13	No
LVVGLCTGQIKTGPAC	(16aa)	14	No

Of the synthesized peptides, Peptide Seq. I.D. No. 2 was most capable of binding to antibodies found in high levels in schizophrenic patients.

EXAMPLE 3: Characterization of Peptide Seq. I.D. No. 2

Laser desorption mass spectroscopy of Peptide Seq. I.D. No. 2 (comprising three cysteins) directly after synthesis shows the presence of a monomer without a ring formation via the cysteins. However, after dissolving the peptide (about 4 mg) in 1 ml water/DMF/DMSO (1:1:1;v:v:v) and leaving the solution overnight at room temperature, the peptide forms a ring via two cysteins and a dimer via the remaining free cystein. No higher polymers could be detected. When testing the binding activity of the two forms of the peptide

to SDA, it became clear that the dimer form of the peptide was much more active in binding SDAs than the non-dimer form.

Chemical analysis of the peptide by reduction, e.g. by mercaptoethanol or sodium borohydrid, destroyed the immunological activity completely, whereas oxidation, e.g. air or oxygen, restored the immunological activity.

EXAMPLE 4: Binding activity of Peptide Seq. I.D. No. 2 to samples from schizophrenic and non-schizophrenic individuals:

The binding activity of Peptide 14 (Seq. I.D. No. 2) to isolated PAAs was tested using the method described above. As seen in Fig. 1A, the above peptide positively bound seven out of eight PAAs obtained from different schizophrenic patients. Fig. 1B shows that the above peptide did not bind PAAs obtained from eight different non-schizophrenic individuals. Peptide Seq. I.D. No. 9 was used as a negative control.

The capability of Peptide 14 (Seq. I.D. No. 2) to bind SDA in plasma samples obtained from schizophrenic patients was then tested. As seen in Fig. 2A, this peptide positively bound four out of five SDA from different schizophrenic patients. Fig. 2B shows that the above peptide did not bind NSDA from fourteen out of fifteen different non-schizophrenic individuals. Peptide 14 (Seq. I.D. No. 9) was used as a negative control.

EXAMPLE 5: Three dimensional structure:

The three-dimensional structure of the antigenic epitope of peptides according to the invention was predicted using a computerized program based on the mineral energy calculations.

As seen in Fig. 3, the predicted structure of the antigenic epitope is a cyclic structure comprising a hydrophobic core and an extension comprising about two positive charges. The positive charged extensions may be positioned in one of many possible spatial orientations.

EXAMPLE 6: Scanning of the surface of the enolase to find epitopes matching the calculated epitopes of the peptides:

The water model three-dimensional structure of the peptides of the invention was calculated. An x-ray three-dimensional structure of enolase generated from a public peptide database was then scanned and the position of the amino acids of the peptides of the invention was compared to the position of the amino acids of the enolase surface to see if an epitope which matches one or more of the calculated epitopes of the peptides of the invention could be found on the surface of the enolase.

As seen in Fig. 4 which is a computer simulation of the scanning of the surface of the enolase, an epitope was found on the surface of the enolase which is comprised of a cluster of hydrophobic amino acids (Leucine, Alanine and Proline) surrounded by positive charged amino acids (Arginine and Hystidine) which matches the epitope simulated from the peptides of the invention. Thus, the predicted structure of the antigenic epitope of the peptides of the invention could indeed be found on the cell surface of enolase.

CLAIMS:

1. A peptide which binds antibodies that are found in elevated levels in body fluids of schizophrenic patients.

2. A peptide according to claim 1, which binds antibodies that are capable of specific binding to a peptide having the amino acid sequence of Seq. I.D. No. 2.

3. A peptide according to claim 1 or 2, which binds antibodies that are capable of binding to a peptide selected from the group, consisting of:

i. SGETEDTFIADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 1)
ii. LVVGLCTCQIKTGPAC (Seq. I.D. No. 2)
iii. IADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 3)
iv. ADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 4)
v. DLVVGLCTGQIKTGAPCR (Seq. I.D. No. 5)
vi. LVVGLCTGQIKTGAPCR (Seq. I.D. No. 6)
vii. LVVGLCTGQIKTGPACR (Seq. I.D. No. 7)
viii. LVVGLCTPQIKTGPACR (Seq. I.D. No. 8)

4. A peptide according to any one of claims 1-3, capable of binding to antibodies which do not bind to peptides selected from the group consisting of:

i. SGETEDTFIADLVVGLCTGQ (Seq. I.D. No. 9)
ii. VVGLCTGQIKTGAPCR (Seq. I.D. No. 10)
iii. CTGQIKTGAPCR (Seq. I.D. No. 11)
iv. LVVGLCTGQIKTGAPC (Seq. ID. No. 12)
v. LVVGLCTGQIKTGAP (Seq. ID No. 13)
vi. LVVGLCTGQIKTGPAC (Seq. ID No. 14)

5. A peptide according to any one of claims 1-4, comprising an amino acid sequence selected from the group, consisting of:

i. SGETEDTFIADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 1)
ii. LVVGLCTCQIKTGPAC (Seq. I.D. No. 2)
iii. IADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 3)
iv. ADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 4)
v. DLVVGLCTGQIKTGAPCR (Seq. I.D. No. 5)
vi. LVVGLCTGQIKTGAPCR (Seq. I.D. No. 6)
vii. LVVGLCTGQIKTGPACR (Seq. I.D. No. 7)
viii. LVVGLCTPQIKTGPACR (Seq. I.D. No. 8).

6. A peptide according to any one of claims 1-4, selected from the group consisting of:

i. SGETEDTFIADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 1)
ii. LVVGLCTCQIKTGPAC (Seq. I.D. No. 2)
iii. IADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 3)
iv. ADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 4)
v. DLVVGLCTGQIKTGAPCR (Seq. I.D. No. 5)
vi. LVVGLCTGQIKTGAPCR (Seq. I.D. No. 6)
vii. LVVGLCTGQIKTGPACR (Seq. I.D. No. 7)
viii. LVVGLCTPQIKTGPACR (Seq. I.D. No. 8)

7. A peptide which binds antibodies that are found in elevated levels in body fluids of schizophrenic patients, said peptide comprising at least one antigenic epitope, said epitope having a cylic three dimenional structure consisting a hydrophobic core and a positively charged extension.

8. An assay for the diagnosis of schizophrenia in an individual, comprising the following steps:

(a) obtaining a sample from said individual being a blood sample, a platelet-containing fraction thereof, or a fraction containing platelet-associated antibodies (PAA) shed from the platelets;

(b) contacting said sample with a peptide capable of binding to antibodies that are found in elevated levels in body fluids of schizophrenic patients.

(c) determining the level of binding of said peptide to said sample, a level higher than the binding level of said peptide to a sample from non-schizophrenic individuals indicating that said individual has a high likelihood of having schizophrenia.

9. An assay in accordance with claim 8, wherein the peptide of step (b) is a peptide having the amino acid sequence of Seq.ID.No.2

10. An assay in accordance with claim 8, wherein the peptide in step (b) comprises an a.a. sequence selected from the group consisting of:

i. SGETEDTFIADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 1)
ii. LVVGLCTCQIKTGPAC (Seq. I.D. No. 2)
iii. IADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 3)
iv. ADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 4)
v. DLVVGLCTGQIKTGAPCR (Seq. I.D. No. 5)
vi. LVVGLCTGQIKTGAPCR (Seq. I.D. No. 6)
vii. LVVGLCTGQIKTGPACR (Seq. I.D. No. 7)
viii. LVVGLCTPQIKTGPACR (Seq. I.D. No. 8).

11. An assay according to claim 8, wherin the peptide in step (b) is a peptide selected from the group consisting of:

i. SGETEDTFIADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 1)
ii. LVVGLCTCQIKTGPAC (Seq. I.D. No. 2)

iii. IADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 3)

iv. ADLVVGLCTGQIKTGAPCR (Seq. I.D. No. 4)

v. DLVVGLCTGQIKTGAPCR (Seq. I.D. No. 5)

vi. LVVGLCTGQIKTGAPCR (Seq. I.D. No. 6)

vii. LVVGLCTGQIKTGPACR (Seq. I.D. No. 7)

viii. LVVGLCTPQIKTGPACR (Seq. I.D. No. 8)

12. An assay in accordance with Claim 8, wherein the peptide in step (b) is a peptide in accordance with claim 7.

13. An assay in accordance with any of Claims 8-12, wherein said sample obtained from the individual is a whole blood sample.

14. A kit for use in the diagnosis of schizophrenia comprising:

i. a support comprising one or more peptides in accordance with any one of claims 1-7 immobilized onto it;

ii. an anti-human immunoglobulin antibody or fragment thereof conjugated to a detectable marker;

iii. reagents required for carrying out the assay, and;

iv. instructions for use.

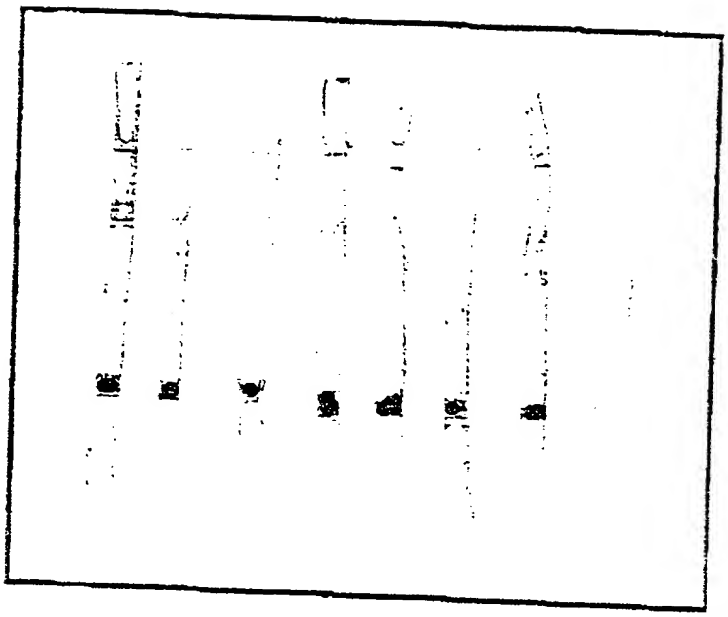

FIG. 1A

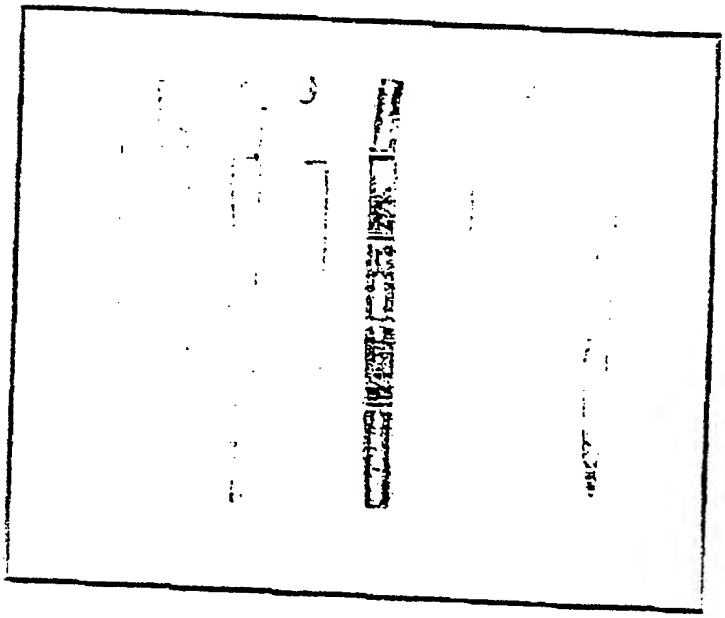

FIG. 1B

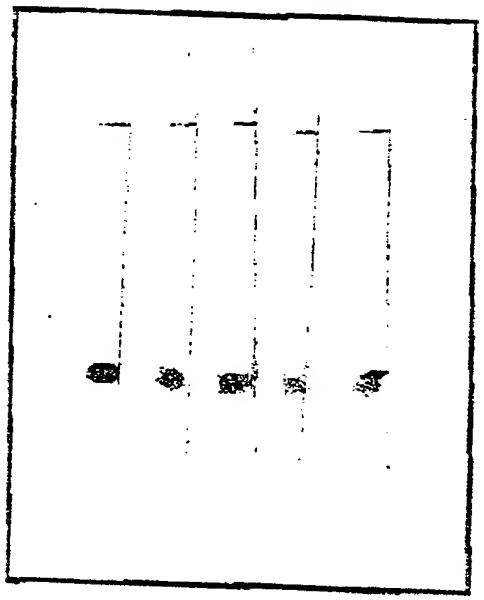

FIG.2A

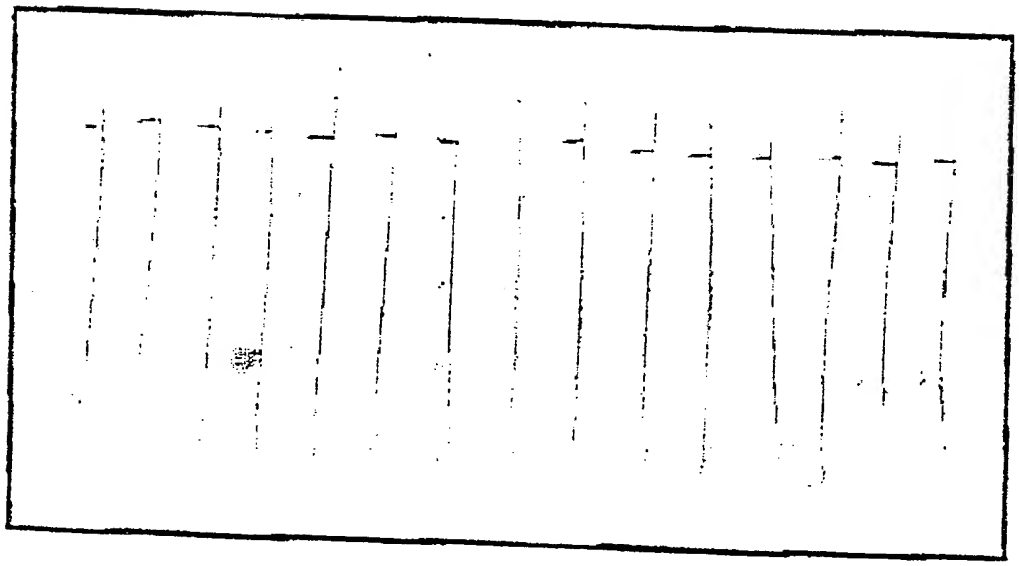

FIG.2B

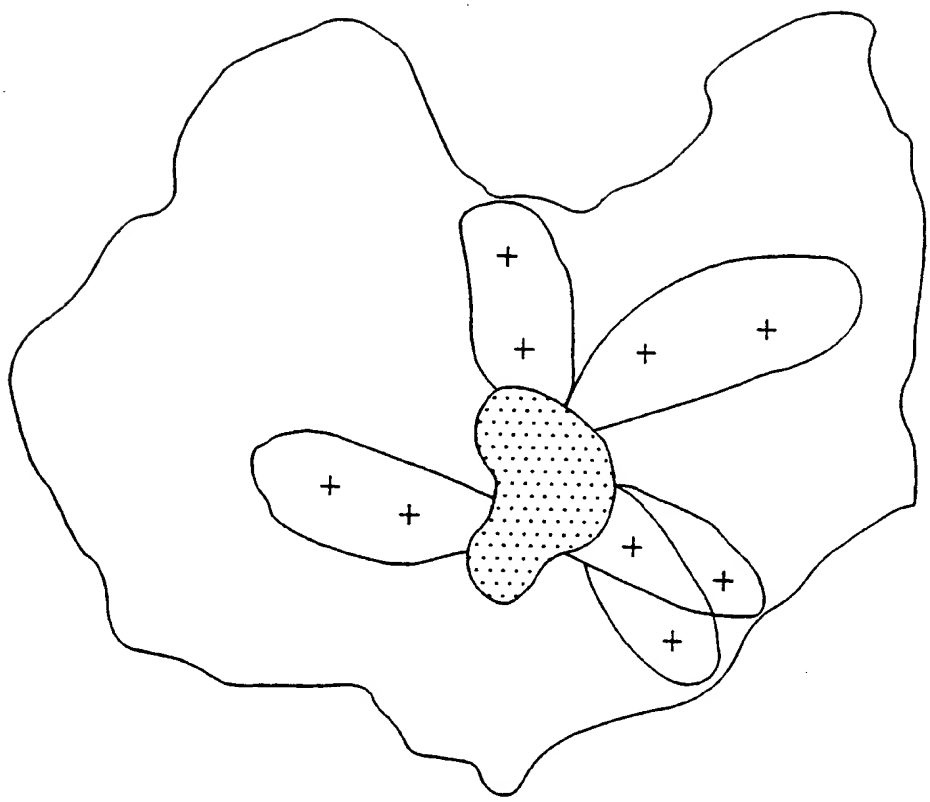

FIG.3

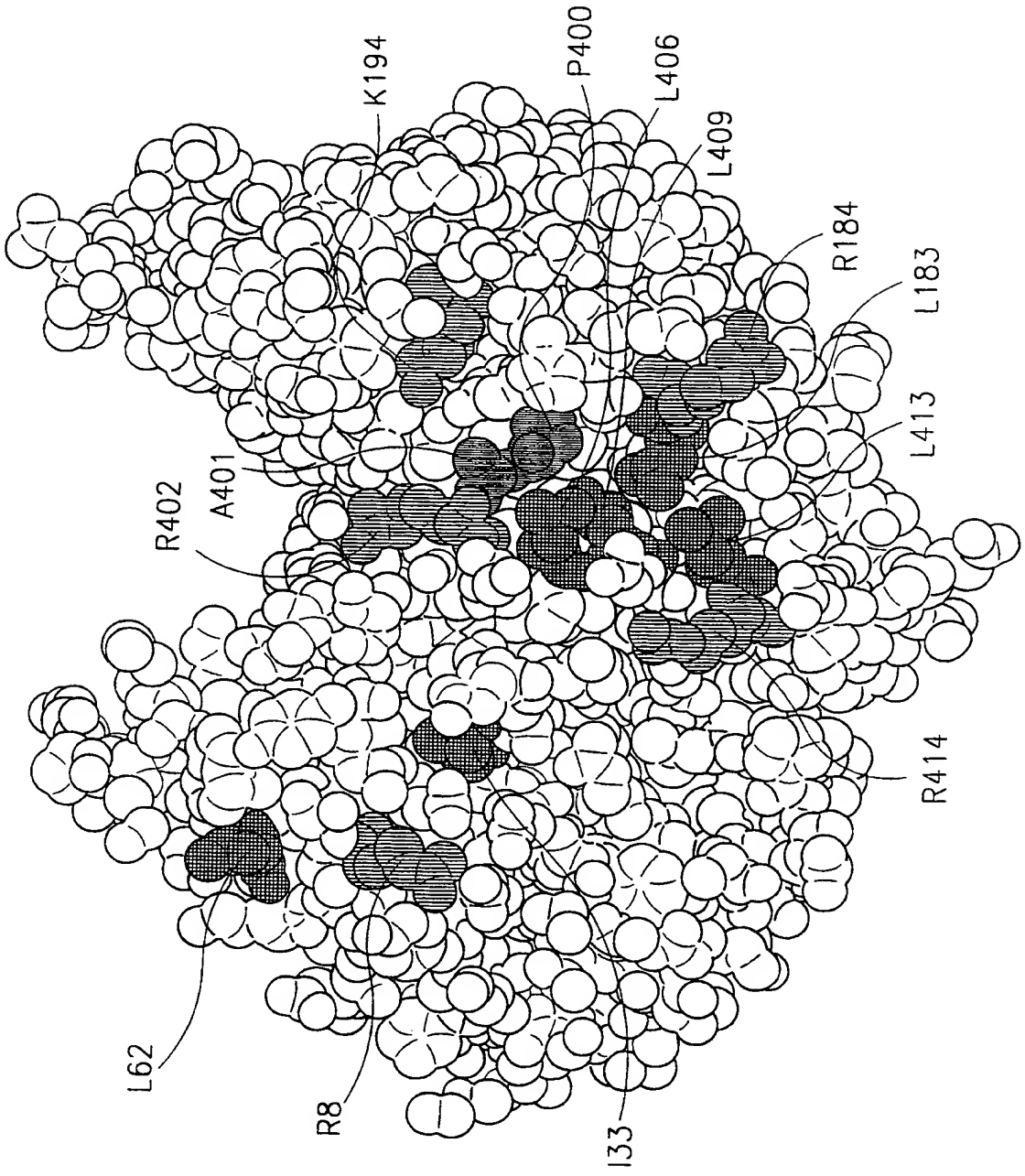

FIG.4

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT:
(A) NAME: YEDA RESEARCH AND DEVELOPMENT COMPANY LTD.
(B) STREET: THE WEIZMANN INSTITUTE OF SCIENCE
(C) CITY: REHOVOT
(E) COUNTRY: ISRAEL
(F) POSTAL CODE (ZIP): P.O.BOX 95
(G) TELEPHONE: +08 9470617
(H) TELEFAX: +08 9470739

(ii) TITLE OF INVENTION: ASSAY FOR THE DIAGNOSIS OF SCHIZOPHRENIA BASED ON A NEW PEPTIDE

(iii) NUMBER OF SEQUENCES: 14

(iv) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30 (EPO)

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

Ser Gly Glu Thr Glu Asp Thr Phe Ile Ala Asp Leu Val Val Gly Leu
1 5 10 15

Cys Thr Gly Gln Ile Lys Thr Gly Ala Pro Cys Arg
20 25

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

Leu Val Val Gly Leu Cys Thr Cys Gln Ile Lys Thr Gly Pro Ala Cys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

Ile Ala Asp Leu Val Val Gly Leu Cys Thr Gly Gln Ile Lys Thr Gly
1 5 10 15

Ala Pro Cys Arg
20

(2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

Ala Asp Leu Val Val Gly Leu Cys Thr Gly Gln Ile Lys Thr Gly Ala
1 5 10 15

Pro Cys Arg

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

Asp Leu Val Val Gly Leu Cys Thr Gly Gln Ile Lys Thr Gly Ala Pro
1 5 10 15

Cys Arg

(2) INFORMATION FOR SEQ ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

Leu Val Val Gly Leu Cys Thr Gly Gln Ile Lys Thr Gly Ala Pro Cys
1 5 10 15

Arg

(2) INFORMATION FOR SEQ ID NO: 7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

Leu Val Val Gly Leu Cys Thr Gly Gln Ile Lys Thr Gly Pro Ala Cys
1 5 10 15

Arg

(2) INFORMATION FOR SEQ ID NO: 8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

Leu Val Val Gly Leu Cys Thr Pro Gln Ile Lys Thr Gly Pro Ala Cys
1 5 10 15

Arg

(2) INFORMATION FOR SEQ ID NO: 9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 amino acids

(B) TYPE: amino acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

Ser Gly Glu Thr Glu Asp Thr Phe Ile Ala Asp Leu Val Val Gly Leu
1 5 10 15

Cys Thr Gly Gln
20

(2) INFORMATION FOR SEQ ID NO: 10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

Val Val Gly Leu Cys Thr Gly Gln Ile Lys Thr Gly Ala Pro Cys Arg
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

Cys Thr Gly Gln Ile Lys Thr Gly Ala Pro Cys Arg
1 5 10

(2) INFORMATION FOR SEQ ID NO: 12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

Leu Val Val Gly Leu Cys Thr Gly Gln Ile Lys Thr Gly Ala Pro Cys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

Leu Val Val Gly Leu Cys Thr Gly Gln Ile Lys Thr Gly Ala Pro
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: unknown
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

Leu Val Val Gly Leu Cys Thr Gly Gln Ile Lys Thr Gly Pro Ala Cys
1 5 10 15